REMARKS

Reconsideration of the allowability of the present application in view of the above claim amendments and the following remarks is requested respectfully.

Discussion of the Claims

In his Action, the Examiner acted upon Claims 1, 2, 4, 5, 20, 23 to 40, 45 to 51, and 55 to 63. In the present Reply, Claim 35 has been cancelled and Claims 64 to 66 have been added. The claims pending presently are Claims 1, 2, 4, 5, 20, 23 to 34, 36 to 40, 45 to 51, and 55 to 65.

Discussion of the Amendments

Claims 23, 24, 28 to 30, 55, and 60 have been amended to clarify that the membrane coating recited therein comprises an ammonio methacrylate copolymer and a plasticizer and that the combined amount of the ammonio methacrylate copolymer and the plasticizer contributes to the particles a weight gain of from about 4% to about 15% of the weight of the cores. Support for this amendment is found in the application at page 11, lines 6 to 8, page 26, lines 8 to 12, and in Tables 4, 5, and 14.

Claims 64 to 66 have been added to define an embodiment of the present invention in which the particles are beads. Support for these claims is in the application at page 3, line 25, page 11, lines 6 to 8, and Claim 35 as filed originally.

Claims 59 and 62 have been amended to define the range of the $AUC_{0-\infty}$ value therein as being from about 128 to about 1,900 ng/ml.h. Support for this

amendment is in the application at Table 23 (see, for example, the $AUC_{0-\infty}$ value with standard deviation for Product B).

Claims 4 and 5 have been amended to depend from Claim 1. Support for these amendments is found in the application at page 4, lines 6 to 13 and 25 to 27.

In addition, amendments of an editorial nature have been made to dependent Claims 56, 58, 61, and 63 so that the language therein is consistent with that of the claims they depend from.

An amendment of an editorial nature has been made to Claim 55 to delete the phrase "and wherein" which appears at the end of the claim. This phrase existed in the claim due to a clerical error.

Amendments of an editorial nature have been made to Claims 34, 60 and 61 so that they properly depend from Claims 24, 59 and 60, respectively, instead of from Claims 25, 58 and 59.

No new matter has been added.

Discussion of the Examiner's Section 103 Rejection
of Claims 23, 24, 28 to 30, 34, 45, 46 and 55 to 58 and 60 to 63

The Examiner rejected Claims 23, 24, 28 to 30, 34, 45, 46, 55 to 58 and 60 to 63 as being unpatentable over the disclosure of U.S. Patent No. 5,958,458 to Norling et al. in view of U.S. Patent No. 6,183,780 to van Balken et al.

The Examiner's rejection is traversed respectfully. In order to establish a *prima facie* case of obviousness, the Examiner must show that the combined

disclosures of the cited references teach or suggest each of the recitations of the claims.

Each of the above claims defines a controlled-release SSRI formulation in which the total amount of an ammonio methacrylate copolymer and plasticizer present in the membrane coating is from about 4% to about 15% of the weight of the cores present in the formulation. The combined disclosures do not disclose such a formulation. The only disclosure anywhere in Norling et al. of a formulation coated with an ammonio methacrylate copolymer and a plasticizer is in Example 10. However, the total amount of copolymer (142.5g dry weight) and plasticizer (28.5g) used therein is 34.2% of the total weight of the cores (500g). As such, the Norling et al. discloses a formulation that is significantly different from that defined by the above claims.

In addition to the above Claims 23, 24, 28 to 30, 34, 45, and 46 each recite very specific release profiles for the formulations defined therein. Because the Norling et al. formulation is significantly different, it exhibits a significantly slower release profile than that recited by the claims (see bottom of Column 32 of Norling et al.).

Van Balken et al. does not solve the deficiencies of Norling et al. as it teaches only delayed immediate release formulations and not a controlled release formulation. Moreover, the combined disclosures of Norling et al. and van Balken et al. do not teach or suggest how one skilled in the art may adjust the amounts of the copolymer and the plasticizer to arrive at a formulation that would provide the release profile recited by Claims 23, 24, 28 to 30, 34, 39, 40, 45, and 46.

Given the above, applicants submit respectfully that the combined

disclosures of the cited art do not render Claims 23, 24, 28 to 30, 34, 39, 40, 45, 46, 55 to 58, and 60 to 63 obvious.

Discussion of the Examiner's Section 103 Rejection
of Claims 1, 2, 4, 5, 20, 25 to 27, 31 to 33, 36 to 40, 47 to 51, and 59

The Examiner rejected Claims 1, 2, 4, 5, 20, 25 to 27, 31 to 33, 36 to 40, 47 to 51, and 59 as being unpatentable over the disclosure of U.S. Patent No. 5,958,458 to Norling et al. in view of U.S. Patent No. 6,183,780 to van Balken et al.

The Examiner's rejection is traversed respectfully. In order for the Examiner to establish a *prima facie* case of obviousness, the Examiner must show that: (A) there is some suggestion or motivation for one skilled in the art to combine the teachings of the cited references to arrive at applicants' invention; and (B) that one skilled in the art would have had a reasonable expectancy that the invention would work for its intended purpose. MPEP §2143. Applicants submit respectfully that the Examiner has failed to show either that there suggestion or motivation to combine the teachings of the cited references to arrive at applicants' invention or that one skilled in the art would have had a reasonable expectancy that the invention would work for its intended purpose.

The Examiner alleges that, as van Balken et al. teaches that fluvoxamine may be used as an anti-depressant in the coated compositions described therein and as Norling et al. discloses coated formulations which may comprise an anti-depressant and may be used for achieving controlled release of an active compound therein, one skilled in the art would have been motivated to use fluvoxamine in the formulation of Norling et al. and arrive at applicants' development.

The Examiner appears to have used an impermissible "obvious to try" rationale in support of her obviousness rejection. While Norling et al. does disclose the use of anti-depressants in the formulations therein, it does not disclose specifically any formulation comprising an anti-depressant and discloses anti-depressants only as possible active agents for use among a long laundry list of other potential active agents for use in the formulation therein (see columns 6, 7, and 8 of Norling et al.). In addition, while Norling et al. does disclose the use of ammonio methacrylate copolymer (one of the coating compounds described as being for use in the formulations of the present invention) as a coating compound, it discloses it among a long laundry list of many other possible coating compounds for use in the formulations therein (see columns 9 and 10 of Norling et al.). Norling et al. does not provide any indication as to what coating compound should be used in a fluvoxamine-containing formulation to allow for the release thereof over a period of not less than 12 hours (as recited by the present claims) or any guidance as to what parameters should be considered in making such a formulation. In fact, the only controlled release formulations disclosed specifically by Norling et al. do not comprise an anti-depressant at all but a bronchodilator, theophylline. As different compounds are expected to have different release rates, such a disclosure alone can not serve as a suggestion that fluvoxamine, when used in the same or similar formulation, would also achieve such a release profile. Van Balken et al. does not remedy the deficiencies of Norling et al. At the very most, the Examiner has only shown that it would have been obvious for one skilled in the art to try fluvoxamine (discussed in van Balken et al.) in the formulations disclosed by Norling et al. The "obvious to try" rationale, however, is an impermissible rationale for use in justifying an obviousness rejection. MPEP §2145X.B.

In addition to the above, even if one skilled in the art substituted fluvoxamine (discussed in van Balken et al.) into the formulation of Norling et al., one skilled in the art would still not have had any expectancy that such a formulation would be successful in releasing fluvoxamine over a period of not less than 12 hours. Applicants do note that Norling et al. discloses a formulation comprising coated theophylline-containing pellets which releases theophylline over a period of not less than 12 hours (see Example 10 thereof). However, one skilled in the art would not have had any expectancy of success that a similar formulation in which fluvoxamine is substituted for theophylline would also result in the release of fluvoxamine over a period of not less than 12 hours. Not only are theophylline and fluvoxamine completely different active agents, one being a bronchodilator and the other being an anti-depressant, but theophylline and fluvoxamine have completely different forms as well. Theophylline is a bicyclic compound without any long chains. Fluvoxamine, on the other hand, contains a benzene ring and two long chains. It simply can not be expected that fluvoxamine can be released at a similar rate as theophylline which has such a vastly different chemical structure. Moreover, the release rate also depends upon the particular atoms present in the compound and how hydrophobic and hydrophilic the compound is. Each of these is affected by the structure of the compound. As such, it can not be expected that fluvoxamine, when substituted for theophylline in the formulation of Norling et al., will be released over a period of not less than about 12 hours following oral administration. Van Balken et al. does not serve to remedy this deficiency. This being the case, one skilled in the art would not have had any expectancy that the use of fluvoxamine in the formulation of Norling et al. would successfully result in a formulation which releases fluvoxamine over a period of not less than 12 hours as required by the claims.

Given the above, the Examiner has failed to show either: (A) that there exists some suggestion or motivation to combine the disclosures of the cited references; or (B) that one skilled in the art would have had an expectancy that the development would successfully work for its intended purpose. Both are required in order to establish a *prima facie* case of obviousness. MPEP §2143. As the Examiner has failed to establish either criteria, she has failed to establish a *prima facie* case of obviousness.

Applicants submit further that the present arguments apply also to the Examiner's obviousness rejection as it relates to Claims 23, 24, 28 to 30, 34, 45, 46, 55 to 58, and 60 to 63.

Discussion of the Examiner's Section 112, First Paragraph, Rejection

The Examiner has rejected Claims 23, 24, 28 to 30, and 55 to 63 under the written description requirement of Section 112, first paragraph, because the Examiner does not consider the "about 4% to about 15%" range recited in the claims to be supported by the descriptive portion of the application. The Examiner alleges that the "about 4% to about 15%" range for the weight gain the membrane coating adds to the weight of core is inconsistent with the "11 to 450%" figure recited on page 13 of the application.

The Examiner's rejection has been overcome by the present amendment to independent Claims 23, 24, 28 to 30, 55, and 60. Claims 56 to 59 are dependent from Claim 55 and Claims 61 to 63 are dependent from Claim 60. The claims have been amended to define the membrane coating as comprising ammonio methaacrylate copolymer (hereafter, "the copolymer") and a plasticizer and to clarify that the combined weight of the copolymer and the plasticizer in a formulation is from about 4% to about 15% of the total weight

of the cores in the formulation. This is supported in the present application in Table 5 which lists the constituents of a particular coating solution for use in a formulation of the present application as being the copolymer (Eudragit), a plasticizer (DBS), and a solvent (I.P.A.). One of skill in the art would understand that the solvent evaporates following the coating of the cores. Thus the total weight of the final coating described in Table 5 consists of the weight of the copolymer and the plasticizer. The application then goes on to state that this coating is applied to the cores at 4%, 6%, 8%, 10%, 12%, and 15%. Thus there is support for the range of about 4% to about 15%. That the percentage amounts refer to the percent the weight of the coating compounds in relation to the weight of the cores is evident from Table 14. In "Batch 5" of the coated fluvoxamine beads listed in Table 14, the total solid weight (following evaporation of the alcohol) of the coating compounds used in the formulation (Eudragit and DBS) is 1.797 kg. This is 11.98% of the 15 kg weight of the cores used in the formulation (described therein as being a "bead"). Similarly, in "Batch 6" of the coated beads listed in Table 15, the total solid weight of the coating compounds used is 2.049 kg, which is 13.66% of the 15 kg weight of the cores used. Further, as shown in Table 7, formulations in which the total amount of copolymer and plasticizer is from about 4% to about 15% of the total weight of the cores exhibit the release profile recited by the claims. For example the "4%" formulation listed therein falls within the scope of Claim 23, the "8%" formulation listed therein falls within the scope of Claim 24, and the "6%" formulation listed therein falls within the scope of Claims 28 to 30.

In addition to the above, the Examiner rejected Claim 59 under the written description requirement of Section 112, first paragraph, because she did not consider the range of the $AUC_{(0-\infty)}$ of from about 275 to about 1,900 ng/ml.h to be supported by the descriptive portion of the application.

The Examiner's rejection is traversed respectfully. This range is supported in Table 23 of the application. The table shows that administration of Product B results in an $AUC_{(0-\infty)}$ of 1014.213 ± 885.705. This means that the administration may result in an $AUC_{(0-\infty)}$ of as low as 128.508 and as high as 1899.918. Administration of Products A, C, and D also result in an $AUC_{(0-\infty)}$ that is within this range. Accordingly, not only is the range of from about 275 to about 1,900 ng/ml.h supported but a range of from about 128 to about 1,900 ng/ml.h is supported as well and the claim has been amended accordingly.

Discussion of the Examiner's Section 112, Second Paragraph, Rejection

The Examiner rejected Claim 55 as being indefinite because of the claim ended with the phrase "and wherein." This was a clerical error and has been corrected in the above amendment.

Conclusion

For the reasons expressed above, applicants request respectfully that the Examiner reconsider and withdraw his rejections. An early and favorable allowance is requested respectfully.

The Examiner is invited to telephone the undersigned to discuss matters that the Examiner believes may be relevant to placing the application in condition for allowance.

Respectfully submitted,

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